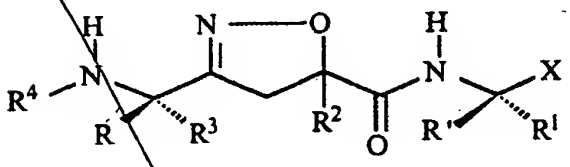
Claims

1. An isoxazoline derivative of the formula (I)



(I)

in which,

R and R' each independently represents hydrogen, simple alkyl chain (-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar);

R^1 represents -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC);

R^3 represents -SAC, -SCAC, -Ar, -SAC-Ar, or side chain of amino acids;

R^2 represents -H, -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), or $-(CH_2)_nOC(=O)R^6$ (in which R^6 = -SAC, -SCAC, -Ar, or -SAC-Ar; and n=1 or 2);

R^4 represents

a) amino acid residue in which ① the carboxyl group attached to the chiral carbon of amino acid is bound to the amine group to form an amide bond, ② the chiral carbon of amino acid has either R or S configuration, ③ the amino group attached to the chiral carbon of amino acid is protected by formyl, acetyl, propyl, cyclopropylcarbonyl, butyl,

methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl or cyclopropylaminocarbonyl, or the amino group may be replaced with a hydrogen atom, and ④ the carboxyl group in the side chain may form an ester group with -SAC or -SCAC,

b) $-C(=O)R^7$ (in which R^7 = -SAC, -SCAC, -Ar, -SAC-Ar), $-CO_2R^8$ (in which R^8 = hydrogen or R^7), $-C(=O)NR^8R^8$, $-SOR^7$, $-SO_2R^7$, or $-C(=O)CH=CH-Ar$,

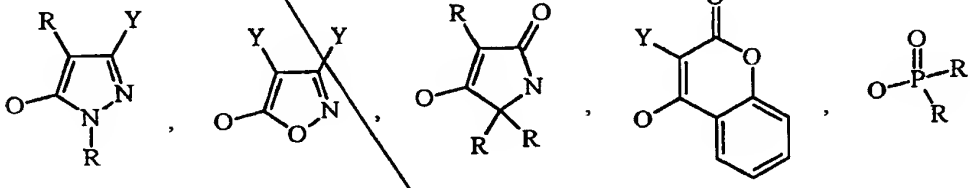
c) $-(C=O)-L-CO_2R^8$, in which L represents a divalent (=capable of double substitution) linker selected from a group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, furan, thiophene, diazole (1,2 or 1,3), triazole (1,2,3 or 1,3,4), tetrazole, oxazole, isoxazole, thiazole, isothiazole, diazine (1,2 or 1,3 or 1,4), triazine, $-Ph(-R^9)-$ (in which R^9 = H, F, Cl, Br, I, CHO, OH, OCH_3, CF_3, OCF_3, CN, C(=O)Me), tetrahydrofuran, tetrahydrothiophene, 1,4-dioxane, $-CH=C(R^{10})-$ (in which R^{10}=H, methyl, ethyl), $-CH=CHCH(R^{10})-$, $-CH(OR^{10})CH_2-$, $-CH_2C(=O)CH_2-$, $-C(=O)CH_2CH_2-$

In cases where R^1 and the adjacent R', and/or R^3 and the adjacent R are connected to each other to form a cyclic compound, R^1-R' or R^3-R together represents $-(CH_2)_n-$, $-(CH_2)_n-O-(CH_2)_m-$, or $-(CH_2)_n-NR^{13}-(CH_2)_m-$ (in which $n+m<9$, R^{13}=-SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, or -C(=O)-SAC-Ar);

X represents -CN, -CHO, $-C(=O)R^{14}$ (in which R^{14} = -SAC, -SCAC, -Ar, -SAC-Ar, or $-CHN_2$), $-C(=O)OR^{15}$ (in which R^{15} = -SAC, -SCAC, -Ar, or -SAC-Ar), $-CONR^{16}R^{17}$ (in which R^{16} and R^{17} each represents -H, -SAC, -O-SAC, -SCAC, -Ar, or -SAC-Ar), $-C(=O)CH_2O(C=O)Ar''$ (in which Ar''

2,6-disubstituted phenyl with F, Cl, Br, I, or CH_3), $-C(=O)CH_2OR^{18}$ (in which R^{18} represents -SAC, -SCAC, -Ar, or -SAC-Ar), or $-C(=O)CH_2OC(=O)R^{19}$ (in which R^{19} = -SAC, -SCAC, -Ar, or -SAC-Ar), or

X represents $-COCH_2-W$, wherein W represents $-N_2$, -F, -Cl, -Br, -I, $-NR^{20}R^{21}$ or $-SR^{22}$ (in which wherein R^{20}, R^{21} and R^{22} each independently represents -SAC, -SCAC, -Ar, or -SAC-Ar or R^{20} and R^{21} are connected to form a cyclic compound); or W represents



in which Y represents -OH, OR^{23} (in which R^{23} = -SAC, or -SCAC), $-C(=O)R^{24}$ (in which R^{24} = -H, -SAC, or -SCAC), -F, -Cl, -Br, -I, -CN, -NC, $-N_3$, $-CO_2H$, $-CF_3$, $-CO_2R^{25}$ (in which R^{25} = -SAC, or -SCAC), $-C(=O)NHR^{26}$ (in which R^{26} = -SAC, or -SCAC), and $-C(=O)NR^{27}R^{28}$ (in which R^{27}, R^{28} = -SAC, or -SCAC) and can be mono- or poly-substituted at its maximum regardless of the order and the kinds, the pharmaceutically acceptable salts, the esters and the stereochemically isomeric forms thereof.

2. The compound of formula (I) according to Claim 1, in which R^4 represents $-C(=O)(CH_2)_pCOOZ$ (in which p is 1 to 4, and Z is hydrogen, -SAC, -Ar or -SCAC).

3. The compound of formula (I) according to Claim 1, in which R^1 represents $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC).

4. The compound of formula (I) according to Claim 1, in which

a) R and R' represent hydrogen,

b) R^1 represents $-CH_2COOH$, $-CH_2COOCH_3$, or $CH_2COOCH_2CH_3$,

c) R^2 represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), SAC, Ar, or Hydrogen,

d) R^3 represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(O)NH_2$ or $-(CH_2)_2C(O)NH_2$,

e) R^4 represents $-C(=O)(O)_nR^{29}$ (in which n=0, 1; R^{29}= -Ar or -SAC-Ar), $-SO_2R^{30}$ (in which R^{30}= -Ar or -SAC-Ar), or $-C(=O)NHR^{31}$ (in which R^{31} = -Ar, or -SAC-Ar), or

f) X represents $-C(=O)CHN_2$, $-C(=O)CH_2Br$, $-C(=O)CH_2Cl$, $-C(=O)CH_2OPh$ or $-C(=O)CH_2OC(=O)Ar''$ (in which Ar"=2,6-dichlorophenyl, 2,6-difluoro-phenyl or 2,6-dimethylphenyl).

5. The compound of formula (I) according to Claim 1, which is selected from the group consisting of the following:

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid;

(2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 1-(N-methyl-N-methoxy)-amide;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro

-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid(LP and MP);
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid(LP and MP);
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid(LP and MP);
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-sulfonylamino)-2-methyl-propyl]-5-phenoxy-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(2S)-2-acetylamino-succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (diasteromeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-imidazolyl-methyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;
(3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-4-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-difluorobenzoylo xy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)- pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dimethylbenzoylo xy)-pentanoic acid[diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-8-carbonylamino)-propyl]-5-phenylmethy l-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl-4, 5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl-4, 5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4, 5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pen

tanoic acid;
(3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-piperidine)-pentanoic acid[diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-pyrrolidine)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-hydroxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(glutaroylamino)-propyl]-5-methyl-4,5-dihydro-iso-xazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid; and
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid methyl ester.

6. A caspase inhibitor which comprises an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof as claimed in any one of Claims 1 to 5.

7. A pharmaceutical composition for treating disease caused by inflammation or apoptosis which comprises as an active ingredient a therapeutically effective amount of an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof as claimed in any of Claims 1 to 5 and pharmaceutically acceptable carrier.

8. The composition according to Claim 7, wherein the disease is selected from the group consisting of the diseases in which cells are abnormally died, dementia, cerebral stroke, brain impairment due to AIDS, diabetes, gastric ulcer, cerebral injure by hepatitis, fulminant hepatic failure (FHF), sepsis, organ transplantation rejection reaction, rheumatic arthritis, cardiac cell apoptosis due to ischemic cardiac diseases and anti-inflammation.

9. The composition according to Claim 7, wherein the disease is fulminant

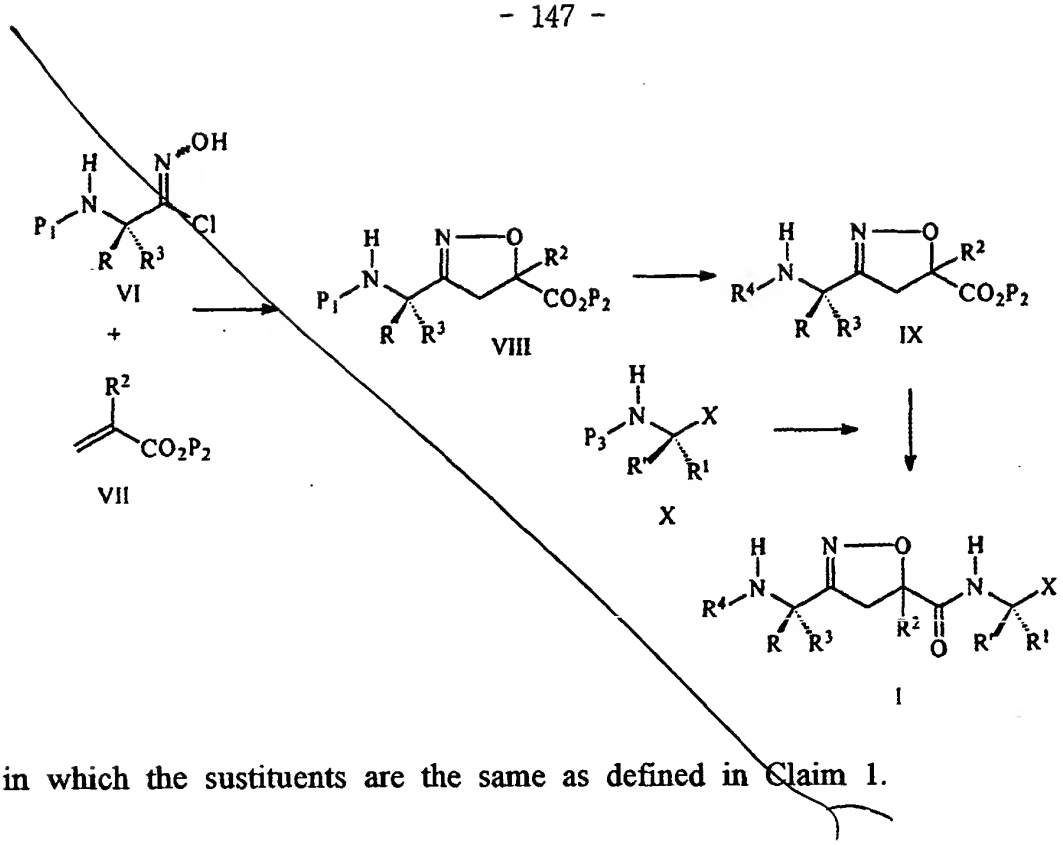
hepatic failure in human.

10. The composition according to Claim 7, in the form for administration orally, percutaneously, or by parenteral injection.

11. A method of treating patients suffering from the diseases caused by caspases activation, which comprises a local or systemic administration of a therapeutically effective amount of an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, the esters or stereochemically isomeric forms thereof, according to any one of Claims 1 to 5 or the pharmaceutical composition according to any one of Claims 7 to 10.

12. A process for preparing the pharmaceutical composition as claimed in any of Claims 7 to 10, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of formula (I) as claimed in any of Claims 1 to 5.

13. A process for preparing a derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof, characterized in that hydroxamoyl chloride (VI) is reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII), and isoxazoline derivative (VIII) is then deprotected and R^4 is introduced therein to give a compound of formula (IX) which is then reacted with a compound of formula (X) and, if necessary, the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and if necessary, the compound of formula (I) having the protecting group P_1 is converted into other compound having substituent R^4.



in which the sustituents are the same as defined in Claim 1.